

AD_____

Award Number: W81XWH-06-1-0401

TITLE: Determinants of Weight Gain in Women with Early-Stage Breast Cancer

PRINCIPAL INVESTIGATOR: Chi-Chen Hong, PhD
Christine Ambrosone, PhD
Dana H. Bovbjerg, PhD
John Cowell, PhD
Stephen Edge, MD
Susan McCann, PhD
Swati Kulkarni, MD
Tracey O'Connor, MD
Jihnhee Yu, PhD

CONTRACTING ORGANIZATION: Health Research Inc.
Buffalo NY 14263

REPORT DATE: April 2009

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release;
distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY) 01-04-2009		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 1 April 08 to 31 March 09	
4. TITLE AND SUBTITLE Determinants of Weight Gain in Women with Early-Stage Breast Cancer				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-06-1-0401	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Chi-Chen Hong, Ph.D. Email: chi-chen.hong@roswellpark.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Health Research Inc Buffalo NY 14263				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research And Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited.					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT. Weight gain after breast cancer diagnosis is common, and has been associated with poorer prognosis. The goals of the study are to examine weight gain relation to treatment-related changes in sex hormone levels, and in relation to genetic polymorphisms in sex hormone pathways, accounting for potential interactions with energy balance, psychosocial factors, tumor characteristics, cancer treatment, and medication use. A prospective longitudinal study of weight gain is being conducted in 215 stage I to IIIA breast cancer patients. To date (3/17/09), 333 participants have been enrolled. To date, 220 out of a possible 266 women have had their 6 months followup visit (82.7%) with 46 (17%) withdrawals. A total of 211 women have been eligible for a 12 month followup, although of this 43 (20%) women have withdrawn, leaving 168 active participants. All of our data has been double entered by two different research associates. We are now currently in the process of data cleaning and are comparing and resolving data entry discrepancies between the double entered data. We have also finished with the DNA extraction process and will begin to genotype our samples. We are now collaborating with Dr. Alice Ceacareanu, from the School of Pharmacy and Pharmaceutical Sciences at the State University of New York at Buffalo, who will now perform the hormone measurements in her laboratory. We have finished optimizing techniques with serum from healthy volunteers, and will begin with study samples shortly. Cortisol-related measurements will now be sent to the Biobehavioral Medicine Core Facility at the University of Pittsburgh Cancer Institute, which is overseen by Dr. Dana Bovbjerg, one of my mentors on the grant.					
15. SUBJECT TERMS Sex hormone, genetic polymorphisms, weight gain, cohort study, diet, physical activity, psychosocial factors.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	15	19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	4
Key Research Accomplishments.....	10
Reportable Outcomes.....	10
Conclusion.....	15
References.....	None

1. Introduction

Weight gain after breast cancer diagnosis is very common, occurring in 50-95% of early stage patients undergoing adjuvant chemotherapy, and has been associated with poorer prognosis. Potentially important contributors to this weight gain may be treatment-related reductions in ovarian function and/or increases in cortisol level due to physical and psychological stress. Since sex hormones and glucocorticoids regulate body weight and adipose tissue distribution, we hypothesize that sex hormones and cortisol play a role in treatment-induced weight gain, and that complex interactions exist with genetic susceptibility, lifestyle, and psychosocial factors. The goals of the study are to examine post-diagnostic weight change and: 1) changes in sex hormone and cortisol levels; 2) genetic polymorphisms in sex hormone pathways; 3) energy intake, physical activity, and psychosocial factors; and 4) characteristics of the cancer and treatments received. A prospective longitudinal study of weight gain is being conducted in 215 patients, aged 18 and older, with non-metastatic breast cancer (Stage I to IIIA). After informed consent, we are collecting serial biospecimens and survey data, to measure hormone levels and genetic polymorphisms, and to assess menopausal status, anthropometry, diet, physical activity, and psychological variables (fatigue, depression, social support) at baseline, 6, and 12 months. These factors will be evaluated in relation to weight changes during and following therapy. This study aims to comprehensively examine predictors and modulators of post-diagnostic weight gain in women with breast cancer using a multidisciplinary approach encompassing hormonal changes, genetic polymorphisms, and psychosocial factors. The outcome of this research may shed light on why so many women experience weight gain after breast cancer and will help guide the development of interventions targeting modifiable risk factors.

2. Body

Task 1: Study Protocol Revisions, Months 1 to 24

Study protocols and the consent form were revised to include DOD elements and were submitted to the USAMRMC Office of Research Protections, Human Research Protections Office (ORP HRPO) for review. Local IRB approval and approval from USAMRMC ORP HRPO was obtained January 8th, 2007. Beginning 10/31/2007 the eligibility criteria for the study protocol was broadened and amended from women aged 35 to 75 to women 18 years and older.

Study protocols have not changed in the past year.

Task 2. Develop databases with Clinical Research Service and Information Technology department at RPCI, months 1-24.

In collaboration with the Clinical Research Services and Information Technology department at Roswell Park, a tracking database has been developed which tracks for each potential participant their study eligibility and participation status. For each participant, the system also tracks specimen collection, as well as allows for entry of all data collected by survey. The database developed uses the eResearch Technology (eRT), eData Management, eStudy Conduct, eSafety Net software products as well as various other RPCI custom applications connected to eRT via Microsoft ODBC technology. The database is currently interfaced to RPCI's hospital information system (demographics), and the RPCI Cerner lab system (lab

results), which allows all of this information to transfer electronically. The database management system is Oracle 9i. Backups of the study data to tape are performed nightly and stored in a separate physical location from the servers themselves.

In the second year we developed a supplementary questionnaire to collect information on temperature perception in breast cancer patients that was initiated July 2007. The questionnaire also collects additional information on vitamin supplement use and use of herbals and other compounds after breast cancer diagnosis. As a result, our study databases were recently updated to allow double entry of this data and we are currently in the process of entering the backlog of data collected with the supplementary questionnaire.

We are now current with our data entry and are now in the process of comparing the double data entries and resolving discrepancies.

Task 3. Train study personnel to consent patients, months 1 to 6

At the start of the study a project co-ordinator was hired and trained to consent patients into the study from the breast clinic at Roswell Park Cancer Institute. In addition, a half-time study coordinator was hired in September 2006 to aid in the conduct of this study.

In January 2009 a new project co-ordinator was hired after our previous coordinator left for a new job position. She was trained to manage the study. In addition we have hired one part-time research assistant to help with patient followup. We are, however, converting this into a full-time research position to allow staff to meet all followup patients in the new Cancer Prevention Research Center at Roswell Park Cancer Institute. This is a dedicated space available to population, behavioral, clinical and basic scientists and designed for conducting prevention research projects. Meeting all study participants at follow-up visits will allow study personnel to check participant questionnaires for completeness and obtain body composition measures on the Tanita scale, which is currently being performed by nurses within the Breast Clinic. We anticipate that meeting participants will reduce attrition rate and reduce the frequency of missing data.

Task 4. Study Recruitment, Months 6-18; Participant Followup, Months 7 to 30.

Recruitment of participants who participate in the Institute's DataBank and BioRepository using consent forms with DOD language was initiated in Jan, 2007. By year 2 (5/14/08), 226 participants had been enrolled. From this group there were a total of 31 withdrawals and 5 individuals were lost to followup leaving 190 active participants.

By the end of year 3 (3/17/09), 333 participants have been enrolled. Of these, 220 out of a possible 266 women have had their 6 months followup visit (82.7%) with 46 (17%) withdrawals. A total of 211 women have been eligible for a 12 month followup, although of this 43 (20%) women have withdrawn, leaving 168 active participants. Reasons for withdrawals in the past year are provided below in table 1. Our plan will be to continue following participants in the upcoming year, which would be expected to yield approximately 75 more participants with one year follow-up data. We will begin meeting all study participants at follow-up visits which we anticipate will reduce the attrition rate and reduce the frequency of missing data. Many of the women who withdraw from the study do so because they are no longer being treated or followed at RPCI and do not live near the Buffalo metropolitan area. Reasons for withdrawals in the past year are given in Table 1.

Table 1. Reasons for Withdrawal from the Study (3/18/08 – 03/23/09)

Reason	Number
Unable/unwilling to make drive to Buffalo or to extra separate visits (includes participants no longer receiving treatment here)	6
Have no time to participate, too tired or too overwhelmed	9
Non compliant, lost to follow-up	18
Not interested in participating with no specific reason provided for decision.	7

Questionnaires provided for self-completion at home

We are in the process of collecting data on dietary intake, physical activity, and psychosocial factors through questionnaires administered at baseline, 6 months, and at 12 months. By the end of year 2, 84% of participants had filled out and returned their baseline questionnaire. The return rate are somewhat lower at 6 and 12 months of followup, being 72% and 67% respectively, with 75% of those eligible for followup data collection returning at least one followup questionnaire. Although the proportion of 75% includes patients who are recently eligible for followup and therefore may not have had sufficient time yet to return their questionnaire, we are in the process of changing our followup protocol to include more frequent contact with participants who do not return their study questionnaire within a month after their provision so that the response rate for the survey component of the study can be improved.

By the end of year 3 (3/17/09), 84% of all participants (257/307) who had not withdrawn within the baseline data collection period (i.e. after being consented but before data collection) have filled out and returned their baseline questionnaire. The return rate for 6 and 12 months of followup, are 74% (162/220) and 79% (133/168) respectively among those who have not withdrawn.

Measurement of weight, height, and body composition

Protocols to measure body composition and weight in the Roswell Park Breast clinic was established using the Tanita Body Composition analyzer, which uses the tetrapolar bioelectrical impedance technique. As well, protocols were established with clinical staff in the Breast Clinic to measure waist and hip circumferences on all newly diagnosed breast cancer patients at baseline and at followup visits. At the end of year 2, 94% of all participants at baseline have provided body composition data using the Tanita scale. For the remaining participants, use of the Tanita scale was either contraindicated, the patient was unable to stand on the scale, or the patient refused the measurement. At 6 months and 12 months of followup, the proportion of those measured by the Tanita scale were lower at 79% and 83% respectively, with 90% of all participants eligible for followup providing at least 1 followup Tanita measurement. Going

forward, our study staff will begin escorting participants personally to the breast clinic to ensure that those eligible for a followup measurement will have these data collected.

At the end of year 3, 93% of participants who had not withdrawn (286/307) had provided baseline body composition measurements using the Tanita Body Composition scale. At 6 and 12 months of followup, proportions of those measured by the Tanita Scale were 80% (177/220) and 85% (145/168), respectively. Last year, we were unable to escort all participants personally to the breast clinic to ensure that all participants received a followup measurement because it was too time consuming for the staff with all their other tasks. We are, however, in the process of hiring a research assistant to allow us to meet all followup patients in the new Cancer Prevention Research Center, a dedicated space established in the past year that is available for conducting prevention research projects. Meeting all study participants at follow-up visits will allow study personnel to check participant questionnaires for completeness and obtain body composition measures on the Tanita scale before proceeding on to the main hospital to the Phlebotomy Clinic for a blood drawn and to the Breast Clinic for their scheduled clinic appointment. We anticipate that meeting participants directly will reduce the frequency of missing body composition data.

Collection of blood and urine samples

Protocols for the collection and processing of fasting blood samples prior to surgery/treatment were developed and include banking of serum, plasma, buffy coat, and red blood cells. As well, presurgical overnight urine specimens were collected, which is accompanied by a specimen questionnaire that was developed, which asks about lifestyle, diet, and medication use in the last 2 days. Currently, fresh whole blood is sent to Labcorp for determination of HbA1C results. Serum and plasma are being stored to allow for future determination of sex hormone and cortisol levels. Originally we had planned to begin shipping serum samples periodically to Labcorp to determine hormone levels beginning in month 6, but to reduce laboratory error we will instead wait until followup is complete and have baseline, 6 months, and 1 year samples assayed simultaneously. At the end of year 2, 98% of all participants had provided a baseline blood sample. At 6 months and 12 months, 85% and 86% of those eligible for followup had provided a blood sample, with 93% of these participants providing at least 1 followup blood sample. For urine samples, 92% of patients provided pretreatment samples (after subtracting those withdrawn from the study) and of these 88% of those eligible for at least one followup urine collection have provided at least one followup urine sample.

At the end of year 3, 94% of participants who have not withdrawn provided a baseline blood sample. At 6 and 12 months, the rates were 87% (191/220) and 95% (159/168), respectively. For urine samples, 90% (275/307) of those who had not withdrawn provided pretreatment samples. At 6 and 12 months, 82% (181/220) and 86% (145/168) provided followup urine samples.

Task 5. Data Management, Months 6 to 31.

We are in the process of double entering all our data into study databases. This is done by at least 2 different individuals, and periodically the two sets of data entered are compared and differences are flagged for further followup.

In the second year, two research associates were hired to help with data entry. Up to November 2007, data entry for the study had been performed largely by student volunteers and

the progress was slow and the study was behind on this task. In response, two half-time research associates were hired between November and December 2007 to aid in data entry and in patient followup. Two persons were required since duplicate data entry had to be performed by different people. In addition to data entry, the two half-time research associates aid in the followup of incomplete questionnaires with participants during evening hours when participants are most likely to be at home, as well as in the scheduling of patients for followup appointments. The additional personnel were needed to handle the increased number of participants requiring active followup.

In year 3, we are current with our double data entry. We are now in the process of cleaning the data by resolving discrepancies found between the two sets of data entered.

Task 6. Measurement of hormone levels, Months 12 to 31.

Currently, fresh whole blood is sent to Labcorp for determination of HbA1C results. Originally we had planned to begin shipping serum samples periodically to Labcorp to determine hormone levels beginning in month 6, but to reduce laboratory error we instead waited until followup is complete and have baseline, 6 months, and 1 year samples assayed simultaneously. Originally we had proposed to use Labcorp to perform all of our hormone measurements, but based on the results of some samples sent from a different study, we were not happy with the reproducibility of measurements. As a result, we are now collaborating with Dr. Alice Ceacareanu in the School of Pharmacy at the University at Buffalo, who will perform the sex hormone assays in her laboratory, and samples for the cortisol-related measurements will now be sent to the Biobehavioral Medicine Core Facility at the University of Pittsburgh Cancer Institute, which is overseen by Dr. Dana Bovbjerg, one of my mentors. We are currently in the process of purchasing Elisa assay kits for in-house sex steroid measurements, which will begin shortly and is anticipated to be complete within 4 months. This will be carried out 573 serum samples, representing all the blood specimens we have collected to date at baseline, 6 months, and 12 months. Arrangements are being currently made to have study samples shipped to the Pittsburgh University Cancer Center for cortisol-related measurements.

Task 7. Postdoctoral Training, Months 1-36

Developmental meetings are held weekly and on an as needed basis to discuss progress and career development with Dr. Christine Ambrosone, the primary mentor. Frequent meetings are also held with other mentors on an as needed basis to address issues associated with the conduct of the study. I have attended several scientific conferences as part of my training including the 2007, 2008, and 2009 Annual Meetings of the American Association for Cancer Research and was the co-chair for 2007 and 2008 for the Annual Grant Writing Workshop for Associate Members, Professional Advancement Session. In 2009, I was co-chair for a Professional Advancement Session “Mentoring and Career Development Plans: Establishing Successful Relationships for Productive Careers”. In 2008, I was invited by AACR to be a junior facilitator at the Leila Diamond Networking Breakfast hosted by Women in Cancer Research at the 2008 AACR Annual Meeting. I attended the AACR Molecular Epidemiology Working Group (MEG) sponsored special conference on ‘Approaches to Complex Pathways in Molecular Epidemiology’ from May 30 to June 2nd, 2007 and attended the 2007 AACR Frontiers in Cancer Prevention Research meeting held from December 5-8, 2007. I continue to attend (and

coordinate) the biweekly Work-in-Progress meetings in epidemiology and chemoprevention that occur within the Department of Cancer Prevention and Control at Roswell Park Cancer Institute, as well as weekly Faculty Forum, Cancer Prevention Grand Rounds, and Medical Grand Rounds seminars. My training has also been greatly enhanced by participating as a peer-reviewer for the DoD BCRP Idea and Synergism grant mechanisms in 2008 and 2009 as well as a reviewer for the Breast Cancer Campaign in the United Kingdom in 2008. I have been invited back in 2009 to participate as a peer-reviewer for the BCRP Idea and Synergism Awards as well as the Pre- and Postdoctoral fellowships in January and May.

Task 8. Mount Sinai Center Visit, Month 12

I have not yet visited Dr. Bovbjerg yet at the Mount Sinai Center in NY and plan this in the upcoming year once the psychosocial data is cleaned and ready for data analysis.

Task 9. Interim Analyses, Months 12-30

We have done analyses to look at data quality and followup rates. We are currently in the process of cleaning our data and will begin analyses focused on our main hypotheses.

Task 10. DNA extraction and Genotyping, Months 14 to 22.

As part of the blood collection protocol, buffy coats are being banked and stored to allow for DNA extraction and genotyping. We have recently completed the DNA extraction for 236 study participants and will begin genotyping proposed polymorphisms in the sex hormone and adrenal hormone pathways.

Task 11. Merge genotyping data with data questionnaires and medical records. Month 23.

We have obtained all the clinical data for all study participants recruited to date and will merge this data with our survey data once the latter is cleaned (currently in process).

Task 12. Final data analysis, interpretation and reporting, Months 31 to 36.

Not yet performed.

3. Key Research Accomplishments.

None yet.

4. REPORTABLE OUTCOMES

4.1. Establishment of Serum and Urine Repository

This research grant has allowed for the creation of a serum and urine repository for the conduct of survivorship studies of breast cancer patients. This biorepository is unique in that it collects biospecimens annually and therefore lends itself well to studies aimed at detecting changes that occur during and after breast cancer treatment.

4.2. Establishment of Study Database

In collaboration with the Clinical Research Services and Information Technology department at Roswell Park, a comprehensive database has been developed which allows for double entry of all data collected by survey. The database developed uses the eResearch Technology (eRT), eData Management, eStudy Conduct, eSafety Net software products as well as various other Roswell Park Cancer Institute custom applications connected to eRT via Microsoft ODBC technology. The database is currently interfaced to RPCI's hospital information system (demographics), and the RPCI Cerner lab system (lab results), which allows all of this information to transfer electronically. The database management system is Oracle 9i. Backups of the study data to tape are performed nightly and stored in a separate physical location from the servers themselves.

4.3. Employment or Research Opportunities

4.3.1. Employment

Based in part on the success of the survivorship cohort developed with this grant and its broad potential as a basis for developing a number of research projects focused on survivorship research in breast cancer patients, I was promoted to an Assistant Member position at Roswell Park Cancer Institute (RPCI) effective Jan 03/08, which is equivalent to a tenure track Assistant Professor at universities. In addition, based on the research funding provided by the DoD and Komen for this project, I was invited to be a member of the Cancer Center Support Grant at RPCI. I also have an appointment as a Research Assistant Professor at the Department of Social and Preventive Medicine at SUNY University at Buffalo, and my application to be an Assistant Professor in the Department of Cancer Pathology and Prevention at Roswell Park was approved.

4.3.2. New Research Opportunities Derived from this Grant

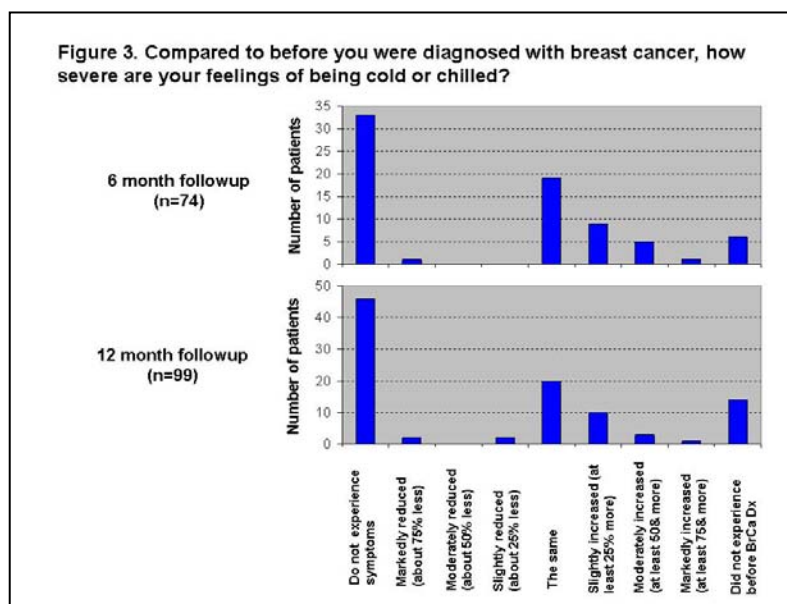
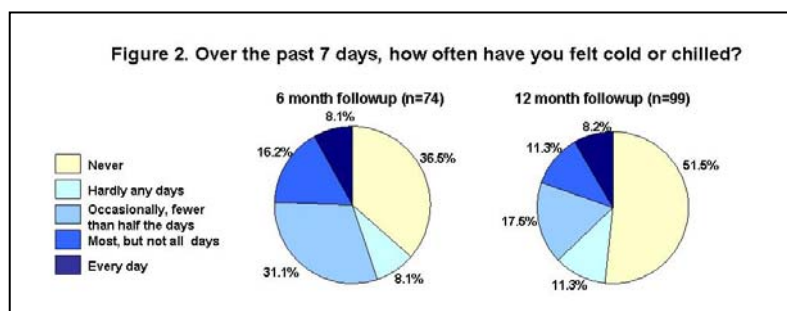
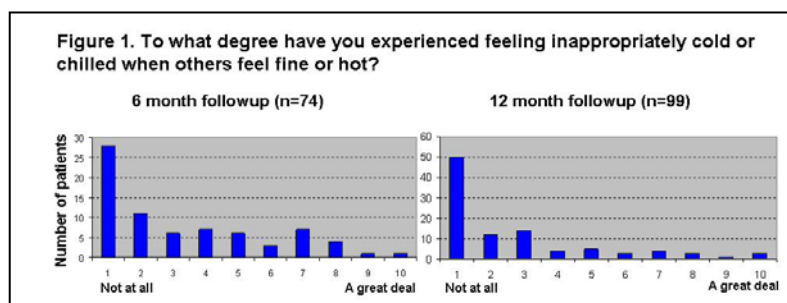
4.3.2.1. Development of Research Studies to Examine Body Temperature Perception and Immune Function following Breast Cancer Diagnosis.

Thermal Discomfort in Breast Cancer Patients after Breast Cancer Diagnosis

The establishment of this cohort of breast cancer survivors has led to a collaboration with Dr. Elizabeth Repasky within the Department of Immunology at the Roswell Park Cancer Institute to explore the hypothesis that a distinct subgroup of breast cancer patients experience symptoms of being persistently cold after breast cancer treatment and that these symptoms are distinct from the more widely studied phenomenon of “hot flashes” as a result of treatment-induced menopause.

In the second year we developed a questionnaire that collects information on women’s experiences with “hot flashes and sweats”, and with feelings of “feeling inappropriately and excessively cold”. The questionnaire collects information about experiences within the past 7 days as well as the past 6 months and was patterned on the Functional Assessment of Cancer Therapy – Fatigue Subscale (FACT-F) and the Multidimensional Assessment of Fatigue (MAF) scales, which are existing validated questionnaires on experiences with fatigue. Information collected includes prevalence and degree of symptoms, severity, severity compared to before their diagnosis with breast cancer, frequency, impact on daily activities, perceived reasons for their experience, and treatments that women have used to try and cope with their symptoms.

From July 2007 to December 2008, we piloted this questionnaire in our cohort of breast cancer survivors. The self-administered questionnaire was completed by 74 study participants 6 months following their initial diagnosis and by 99 participants one year following their diagnosis (which included many of the same participants who completed the 6 month questionnaire). Our



findings, shown in Figures 1 and 2, indicate that a substantial portion of women diagnosed with early-stage breast cancer reported that they felt cold at least occasionally in the past 7 days at either 6 or 12 months after their breast cancer diagnosis (55% at 6 months and 37% at 12 months). When women who reported experiencing “feeling cold or chilled” in the past 6 months were asked to compare the severity of their current experience to that before their breast cancer diagnosis (see Figure 3), 8.1% and 14.3% of women at 6 and 12 months, respectively, reported that they did not experience feeling chilled prior to their diagnosis and 20.4% and 14.3%, respectively, reported feeling slight to marked increases. About 70% of women either indicated that the experiences were “the same” or that they “did not experience feeling cold or chilled”. These data suggest that a subset of women do appear to feel inappropriately cold following their diagnosis and treatment for breast cancer.

Body temperature changes in breast cancer patients

In addition we examined body temperature changes in two populations of breast cancer patients at RPCI. Initially, 56 breast cancer patients diagnosed at RPCI between Jan 2001 and Dec 2003 were examined to determine whether body temperature changed after breast cancer diagnosis, and found significant declines over a 1 year follow-up period. Body temperatures were abstracted from medical charts and a statistically significant decline in unadjusted body temperature was observed at 6 (-0.22°C, p=0.01) and 12 (-0.29°C, p=0.003) months after diagnosis (see Table 1). Declines at 12 months were found to be significantly associated with

younger age at diagnosis after adjusting for menopausal status, date of diagnosis, and cancer treatments received, but body temperature was not shown to vary with radiation treatment, chemotherapy treatment or hormonal therapy (Table 2).

These findings were in part replicated

recently when we examined body temperature for 186 breast cancer patients participating in the cohort of women participating in the Women’s Health after Breast cancer Study, diagnosed between Feb 2006 and March 2008. Body temperature data at the time of diagnosis, and 6 and 12 months post-diagnosis were abstracted from medical records and a statistically significant decline in unadjusted body temperature was observed at 12 months after initial diagnosis (-0.13°C, 95% CI -0.21, -0.05, p=0.001) (see Table 3). Declines at 12 months were found to be

Body Temperature in 56 Breast Cancer Patients Diagnosed Between Jan 2001 and December 2003 at RPCI

Table 1. Mean Body Temperature at Diagnosis and 6 and 12 months							
	Body Temperature °C (95% CI)		Temperature Difference from Dx °C (95% CI)		Paired t-test	P	
Diagnosis (Dx)	36.75 (36.62, 36.89)						
6 months	36.53 (36.39, 36.67)		-0.22 (-0.39, -0.05)		-2.63	0.01	
12 months	36.46 (36.32, 36.60)		-0.29 (-0.48, -0.10)		-3.09	0.003	

Table 2. Differences in Body Temperature 6 and 12 months after Breast cancer Dx According to Age for 56 Patients Diagnosed between Jan 2001 and December 2003							
6 Months after Dx					12 Months after Dx		
Age (yrs)	N	Temp Difference from Dx °C (95% CI)	F	P	Temp Difference from Dx °C (95% CI)	F	P
40-50	21	-0.40 (-0.85, 0.05)	0.77	0.47	-0.51 (-0.98, -0.03)	3.76	0.03
51-60	23	-0.03 (-0.52, 0.45)			0.05 (-0.46, 0.57)		
60+	12	-0.07 (-0.67, 0.53)			0.51 (-0.12, 1.14)		
		P-trend=0.57			p-trend=0.008		

significantly associated with younger age at diagnosis (≤ 50 yrs) as well as older age at diagnosis (60+) after adjustments for cancer treatments received, although body temperature was not shown to vary with radiation treatment, chemotherapy treatment, or hormonal therapy (Table 4). These results, together, suggest that changes in body temperature regulation may indeed occur in breast cancer patients after their diagnosis, although the cause is unclear. These data do indicate that further study is warranted on determining the clinical implications of these observations, if any.

Coupled with preliminary data in mice generated in Elizabeth Repasky's research group showing that core body temperatures drop during tumor growth and that support of body temperature *alone* significantly delays and/or reduces tumor growth (Fig 4), we have been invited to submit a full application for the 2009 DoD Impact award. We are proposing a complementary series of population-, clinical-, and experimental-based studies to comprehensively explore the hypothesis that variation in body temperature and/or thermal discomfort experienced by breast cancer survivors may be an indicator of underlying immune function and may be associated with risk of recurrence. More importantly, we postulate that these relationships can be manipulated by adopting measures to support body temperature, and hypothesize that nightly hot baths, particularly in the evening, may lead to improvements in quality-of-life, sleep quality, immune function, and lower risk of breast cancer recurrence. If successful, these studies may reveal thermoregulation as a new target of therapeutic intervention, which could have immediate clinical application, resulting in significant and immediate improvements to patient prognosis and quality-of-life. Particularly exciting is the collaboration formed with Dr. Alice Ceacareanu in the School of Pharmacy at the University at Buffalo to develop an approach for assessing patient serum-induced chemotaxis exerted on a highly metastatic breast cancer cell line, as an *in vitro* indicator of invasive potential that might be related to risk of recurrence. If this relationship is prospectively confirmed in future studies, it will be an extremely useful biomarker of recurrence risk, and will potentially allow for patient specific evaluation of the effectiveness of various risk

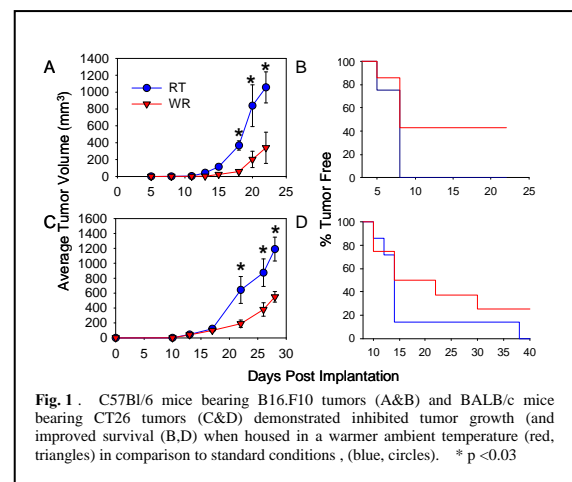
Body Temperature in 186 Breast Cancer Patients Diagnosed Between February 2006 and March 2008 at RPCI in the Women's Health after Breast Cancer Study

Table 3. Mean Body Temperature at Diagnosis and 6 and 12 months

	Body Temperature °C (95% CI)	Temperature Difference from Dx °C (95% CI)	Paired t-test	P
Diagnosis (Dx)	36.49 (36.42, 36.56)			
6 months	36.43 (36.37, 36.50)	-0.05 (-0.14, -0.03)	-1.20	0.23
12 months	36.35 (36.28, 36.42)	-0.13 (-0.21, -0.05)	-3.34	0.001

Table 4. Differences in Body Temperature 6 and 12 months after Breast cancer Dx According to Age

6 Months after Dx					12 Months after Dx		
Age (yrs)	N	Temp Difference from Dx °C (95% CI)	F	P	Temp Difference from Dx °C (95% CI)	F	P
≤ 50	78	-0.20 (-0.34, 0.06)	3.33	0.04	-0.25 (-0.38, -0.12)	5.77	0.004
51-60	54	0.12 (-0.04, 0.29)			0.08 (-0.06, 0.23)		
60+	54	-0.01 (-0.17, 0.15)			-0.17 (-0.31, -0.03)		



modification strategies and therapies. An R21 grant has recently been submitted to test the hypothesis that nightly hot baths as a strategy to support body temperature in breast cancer patients will result in improvements in immune function, better sleep quality, reduced fatigue and better quality-of-life, fewer symptoms of thermal discomfort, and lower indices of serum-induced chemotaxis of a breast tumor cell line, possibly indicating lower risk of cancer metastasis.

Pending Grants:

NIH, R21 (Hong, Ceacareanu co-PI; 30%)	12/01/09 – 11/30/11 \$500,000 (direct)/\$871,065 (total)
--	---

Nightly baths: A strategy for altering immune function in breast cancer survivors

Study Goal: We propose to conduct a highly novel randomized intervention study to assess taking nightly hot baths as a strategy for improving immune function and reducing risk of breast cancer recurrence. We hypothesize that women receiving daily hot bath treatments will show improvements in immune function, better sleep quality, reduced fatigue and better quality-of-life, fewer symptoms of thermal discomfort, and lower indices of serum-induced chemotaxis of a breast tumor cell line, possibly indicating lower risk of cancer metastasis.

4.3.2.2. Research Study to Examine Determinants of Urinary Isothiocyanate Levels

Urine biospecimens collected in this study have been analyzed by a Postdoctoral Fellow, Dr. Li Tang, under the mentorship of Dr. Christine Ambrosone to examine determinants of dietary isothiocyanates levels in urine samples. Dietary isothiocyanates (ITCs) are a group of promising cancer-chemopreventive agents widely found and consumed in cruciferous vegetables. In order to fully understand the cancer-protective effect of ITCs in humans, accurate capture of dietary ITC intake is critical. This study is the result of a collaboration between Drs. Li Tang, Christine Ambrosone, Yuesheng Zhang, Susan McCann, Lara Sucheston, and myself at Roswell Park Cancer Institute. The study focuses on using 150 banked pre-treatment urine and plasma samples along with linked questionnaire data from the study cohort established with the DoD Determinants of Weight Gain grant. The study will use urinary total ITC levels as a biomarker of ITC exposure to evaluate three important issues: 1) to determine the relationship between total urinary ITCs and dietary intake of ITCs as well as cruciferous vegetable intake estimated from a food frequency questionnaire; 2) to define the ranges of dietary, plasma, and urinary total ITCs in a Caucasian population located in the United States; 3) to examine the effect of polymorphisms of genes (GST, γ -GT, CG, and NAT) on ITC metabolism. To the best of our knowledge, the proposed study has never been performed and will provide important information for future studies examining the role of ITCs in cancer prevention and in survival. Funding for this research is being provided by an institutional NCI R25 Cancer Prevention Postdoctoral Training Grant. Urinary ITC measurements are complete and are currently being analyzed with respect to dietary data.

4.3.2.3. Genetics of Cancer-Related Fatigue: a Pilot Study

We are collaborating with Dr. Hua Zhao, a molecular epidemiologist in the Department of Cancer Prevention and Control at Roswell Park Cancer Institute, to investigate the relationship between oxidative stress in breast cancer patients and cancer related fatigue. This innovative and

important area proposed by Dr. Zhao has not yet been investigated. Dr. Zhao is in the process of evaluating oxidative stress biomarkers (copy number of mitochondrial, mitochondrial DNA damage, lipid peroxidation, and total antioxidant levels) in 100 study participants at baseline and 12 months after diagnosis. We will test whether oxidative stress biomarkers can be predictors of cancer related fatigue in these breast cancer patients.

5. Conclusion

In the upcoming year we will continue followup of study participants, perform our hormone assays and genotyping. Data cleaning is currently ongoing and once finished will allow for data analysis and manuscript preparation. Findings from this study will help identify women who are most susceptible to weight gain after being diagnosed with breast cancer, based on biologic characteristics as well as modifiable factors. From a public health viewpoint, findings from this study may indicate ways to improve women's health after breast cancer and to optimize their long-term survival.

6. References

None